DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-264

Bertek Pharmaceuticals, Inc.
Attention: Andrea B. Miller
Director, Regulatory Affairs
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310

Dear Ms. Miller:

Please refer to your new drug application (NDA) dated December 31, 2002, received January 2, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Apokyn (apomorphine hydrochloride) 10 mg/ml Injection.

We acknowledge receipt of your submissions dated:

October 17, 2003	January 16, 2004	February 17, 2004	February 26, 2004
March 2, 2004	March 5, 2004	March 12, 2004	March 29, 2004
March 29, 2004	April 12, 2004	April 14, 2004	

The October 17, 2003 submission constituted a complete response to our July 2, 2003 action letter.

This new drug application provides for the use of Apokyn (apomorphine hydrochloride) Injection for the acute, intermittent treatment of hypomobility, "off" episodes ("end-of-dose wearing off" and unpredictable "on/off" episodes) associated with advanced Parkinson's disease.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the enclosed draft labeling. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert, text for the patient package insert, Ampule and Pen Medication Guides) and submitted labeling (immediate container and carton labels submitted October 17, 2003). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this

submission "**FPL for approved NDA 21-264.**" Approval of this submission by FDA is not required before the labeling is used.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are waiving the pediatric study requirement for this application.

POSTMARKETING COMMITMENTS

We remind you of your postmarketing study commitments submitted in your April 14, 2004 submission. These commitments are listed below.

PHARMACOLOGY/TOXICOLOGY
Commitment #1:

You have committed to conduct one long term carcinogenicity study of subcutaneous apomorphine in rats to assess the carcinogenic potential of apomorphine. Prior to study initiation, submit the proposed development plan for the carcinogenicity evaluation of apomorphine and the specific study protocol for the Agency's review to assess whether or not the proposed study is adequate to meet scientific and regulatory requirements as well as the Agency's expectations.

Final Report Submission Date: May 2008

Commitment #2:

You have committed to conduct one long term carcinogenicity study of subcutaneous apomorphine in mice to assess the carcinogenic potential of apomorphine. Prior to study initiation, submit the proposed development plan for the carcinogenicity evaluation of apomorphine and the specific study protocol for the Agency's review to assess whether or not the proposed study is adequate to meet scientific and regulatory requirements as well as the Agency's expectations.

Final Report Submission Date: May 2008

Commitment #3:

You have committed to repeat the previously conducted in vivo micronucleus test using a multiple dosing regimen post approval. Due to the nature of this request and the significance of the multiple dosing regimen on bone marrow/erythrocyte harvest and evaluation, the division will review the proposed study protocol to assess whether or not the design is adequate to meet scientific and regulatory requirements as well as the Agency's expectations prior to study initiation.

Final Report Submission Date: November 2004

Commitment #4:

You have committed to conduct a reproductive toxicity study in rats to assess the potential effects of apomorphine on fertility and early embryonic development pursuant to guidelines set forth in ICH S5A (1994) and S5B (1996).

Final Report Submission Date: May 2005

Commitment #5:

You have committed to conduct a reproductive toxicity study in rats to assess the potential effects of apomorphine on embryo-fetal development in accordance with guidelines set forth in ICH S5A (1994).

Final Report Submission Date: November 2005

Commitment #6:

You have committed to conduct are productive toxicity study in rabbits to assess the potential effects of apomorphine on embryo-fetal development to assess the potential effects of apomorphine in accordance with guidelines set forth in ICH S5A (1994).

Final Report Submission Date: November 2005

Commitment #7:

You have committed to conduct a reproductive toxicity study in rats to assess the potential effects of apomorphine on prenatal and postnatal development including maternal function in accordance with guidelines set forth in ICH S5A (1994). Prior to study initiation, submit the proposed study protocol for the Agency's review to assess whether or not the proposed study is adequate to meet scientific and regulatory requirements as well as the Agency's expectations.

Final Report Submission Date: November 2005

Commitment #8:

You have committed to the conduct of a ^{14}C-apomorphine mass balance study in rats to assess the metabolic pathway and routes of elimination for apomorphine and its major circulating metabolites.

Final Report Submission Date: May 2005

Commitment #9:

You have committed to the conduct of a ^{14}C-apomorphine mass balance study in mice to assess the metabolic pathway and routes of elimination for apomorphine and its major circulating metabolites.

Final Report Submission Date: May 2005

Commitment #10:

You have committed to the conduct of a ^{14}C-apomorphine mass balance study in monkeys to assess the metabolic pathway and routes of elimination for apomorphine and its major circulating metabolites.

Final Report Submission Date: August 2005

CLINICAL
Commitment #1:

You have committed to the conduct of a clinical trial designed to assess the potential effects of apomorphine on the QTc interval. Due to the complexity of the design of this study, submit the protocol for review and discussion prior to study initiation.

Protocol Submission Date:	October 2004
Study Start Date:	April 2005
Final Report Submission Date:	October 2006

Commitment #2:

You have committed to the conduct of a randomized placebo-controlled trial to investigate the actual necessity for the use of concomitant trimethobenzamide to decrease nausea and vomiting in patients, who initiate and continue treatment with apomorphine. In addition this trial would also be designed to address the risk / benefits of trimethobenzamide 300 mg.

Protocol Submission Date:	October 2004
Study Start Date:	April 2005
Final Report Submission Date:	April 2007

Commitment #3

You have committed to submit the final Clinical Study Report for APO304 (Syringe to Pen Patient Transfer Study in 20 Patients) by June 2004.

Commitment#4

You have committed to submit a safety update for approximately 80 patients in APO-401 who have been switched from the ampule/syringe to the cartridge/pen by December 2004 (the date that the last patient will complete this study is October 2004).

Commitment #5

You have committed to provide the Agency a proposal and design and feasibility plan for a revised pen by October 2004.

CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS
Commitment #1:

You have committed to conduct a ^{14}C-apomorphine mass balance study in 6 healthy humans to assess the metabolic pathway and routes of elimination for apomorphine and its major circulating metabolites. This study will also determine the apomorphine plasma protein binding in these subjects.

Protocol Submission Date:	December 2004
Study Start Date:	April 2005
Final Report Submission Date:	June 2006

Commitment #2:

You have committed to perform a pharmacokinetic study addressing the differential effects of 250 mg three times a day (TID) versus 300 mg TID dosing regimens of trimethobenzamide on the pharmacokinetics of apomorphine. This study will only address the differential effect of the two trimethobenzamide dosing regimens on apomorphine and will not include patients treated with apomorphine without an anti-emetic.

Protocol Submission Date:	July 2004
Study Start Date:	October 2004
Final Report Submission Date:	November 2005

Commitment #3:

You have committed to conduct a pharmacokinetic and pharmacodynamic study to assess the drug interaction potential of apomorphine with alcohol and antihypertensives to include vasodilators (including short-and long-acting nitrates).

Protocol Submission Date:	September 2004
Study Start Date:	December 2004
Final Report Submission Date:	6 months after study completion

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled "**Postmarketing Study Protocol**", "**Postmarketing Study Final Report**", or "**Postmarketing Study Correspondence**."

In addition, submit three copies of the introductory promotional materials that you propose to use for this/these product(s). Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division/ the Division of DIVISION NAME and two copies of both the promotional materials and the package insert(s) directly to:

Division of Drug Marketing, Advertising,
and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at www.fda.gov/medwatch/report/mmp.htm.

If you have any questions, call CDR Teresa Wheelous, Sr. Regulatory Management Officer, at (301) 594-2850.

Sincerely Yours

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Robert Temple

4/20/04 07:18:41 PM